

## REMARKS

Claims 1-16 are pending; of these, claims 5-12 are withdrawn. Claims 1-4 and 13-16 are subject to final rejection. *No amendments to the claims are submitted herewith.* Reconsideration and allowance of the claims are respectfully requested.

### Rejection under 35 U.S.C. §112—Written Description

Claims 1 and 16 are rejected as failing to comply with the written description requirement. The Office action provides no basis for this rejection of claim 1. It is the Office's burden to support such a rejection (MPEP2163.04). Because the Office has not met this burden, Applicants respectfully assert that the instant rejection of claim 1 is unsupported and should be withdrawn.

With regard to claim 16, the Office alleges that “a method wherein the non-acidified sodium nitrite is administered to the subject in an amount and for a sufficient period of time to reach a circulating concentration in blood of the subject in less than about 25  $\mu\text{M}$ , thereby treating or ameliorating the condition” is not adequately described in the specification. Applicants understand this rejection is based on the phrase “less than about 25  $\mu\text{M}$ ”.

Applicants respectfully assert that claim 16 (and claim 1) is fully and completely described in the specification as filed. Applicants thank the Examiner for acknowledging (at page 3 of the current action) that *in haec verba* written support is not necessary for a limitation, rather “an explicit or implicit suggestion by the disclosure” is sufficient. The concentration of non-acidified nitrite in the circulating blood listed in claim 16 (25  $\mu\text{M}$ ) is supported at least implicitly by Applicants disclosure. For instance, on page 12, lines 30-34, the specification indicates that “pharmaceutically-acceptable salts of nitrite (such as sodium nitrite) are effective as vasodilators at calculated dosages of about 0.6 to about 200  $\mu\text{M}$  final concentration in the circulating blood of a subject”; similarly, on page 19, lines 8-9, Applicants state “[i]n certain examples, the sodium nitrite is administered to a circulating concentration of about 0.6 to 240  $\mu\text{M}$ .” Additionally, the examples describe administration of non-acidified sodium nitrite to subjects to concentration in the circulating blood of up to at least 221.82  $\mu\text{M}$  (see page 39, line 36; the nitrite is administered in sodium bicarbonate buffer at pH 7.0-7.4, see page 37, lines 1-3). See also Figure 13D and the accompanying text (*e.g.*, Example 3), which tracks plasma nitrite after inhalation of non-acidified sodium nitrite; the level is between about 30  $\mu\text{M}$  and 15  $\mu\text{M}$ . Thus, implicit support is clearly present in the specification for circulating levels of non-acidified

sodium nitrite at least at any level between 0.6  $\mu\text{M}$  and 221.82  $\mu\text{M}$ , with representative specific examples throughout this range.

Thus, the embodiments encompassed by claim 16 (and claim 1) were fully described in the specification as filed. Applicants therefore request withdrawal of this rejection.

### **Rejection under 35 U.S.C. §103(a)**

Claims 1-4 and 13-15 are rejected as allegedly obvious over Zhang *et al.* (1994) (“Zhang”) in view of Modin *et al.* (2001) (“Modin”). Applicants traverse, both for the reasons previously made of record and as follows.

#### *The Office has not Properly Established a Prima Facie Case of Obviousness*

Applicants respectfully submit that the Office has not properly determined the scope and content of the cited references. Because of this, the Office has overlooked differences between the claims and the cited references that make clear that there could have been no reasonable expectation that one of ordinary skill in the art could have predictably reached Applicants’ invention based on a combination of the teachings of the cited references. These differences are explored below, and in the five accompanying Declarations under 37 C.F. R. §1.132

The Office characterizes the content of the cited references as follows (though Applicants do not admit to the accuracy of these characterizations): Zhang teach administration of the nitric oxide (NO) donors (that is, sodium nitroprusside and 3-morpholino-sydnonimine) to rats to increase blood flow and reduce brain damage due to focal ischemia; Modin teaches that (i) NO is derived from nitrite (citing the title of Modin); (ii) non-acidified nitrite “has relaxatory effects similar to “acidified” nitrite” (citing figures 1, 2, and 5, and the accompanying text), with a threshold response of 10  $\mu\text{M}$  and near relaxation to basal tone at 1000  $\mu\text{M}$  (citing page 11, results); and (iii) that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during ischemia/hypoxia (citing page 15, last paragraph). According to the Office, the difference between claims 1-4 and 13-15 and Zhang is an express teaching of non-acidified sodium nitrite in the amount of 0.6 to 240  $\mu\text{M}$ , which deficiency is allegedly cured by Modin. The Office claims that one of skill in the art would be motivated to combine the teachings of Zhang and Modin because “Zhang et al. suggest using other nitric oxide

donors and Modin et al[.] suggest how much sodium nitrite would be beneficial in tissues during ischemia.”

However, Applicants respectfully assert that the skilled artisan would not have come to the same conclusions as the Office regarding the teachings of Zhang and Modin. First, **“nitric oxide donors” (as that phrase is used in Zhang) and sodium nitrite are not equivalent substitutes for each other.** Thus, one of skill in the art, reading Zhang, would not consider that the “other nitric oxide donors” referred to by Zhang would include sodium nitrite. Second, **the aortic ring bioassays used by Modin are not predictive of the *in vivo* effects of sodium nitrite.** Thus, one of skill in the art would not understand that the teachings of Modin are applicable to an *in vivo* setting. Because of these significant differences, the skilled artisan would not find claims 1-4 and 13-16 obvious over Zhang in view of Modin.

In support of these assertions, Applicants provide herewith the Declarations of five scientists who were working the relevant field during the time that Zhang and Modin were published. Included in this group are: Dr. Bruce Freeman, Dr. Malte Kelm (who is senior author of the Lauer *et al.* reference, which was previously made of record and is discussed below), Dr. Bruce King, Dr. Louis Ignarro (who received a Nobel Prize in Physiology for work related to the physiological effects of nitric oxide, and is the submitting editor for the Lauer *et al.* reference) and Dr. Jon Lundberg (the senior author of the Modin *et al.* reference). Each of these scientists has at least 15 years of experience in research, including work on the physiological effects of nitric oxide and inorganic nitrite and in particular the effects of these molecules on vascular tone (see paragraph 2 of the Freeman, Kelm, King, Ignarro and Lundberg Declarations). None of these scientists has a financial interest in the instant patent application (see paragraph 1 of the Freeman, Kelm, King, Ignarro and Lundberg Declarations).

**(1) “Nitric oxide donors” (as that phrase is used in Zhang) and sodium nitrite are not equivalent substitutes for each other**

Zhang describe use of the nitric oxide donors sodium nitroprusside (SNP) and 3-morpholino-sydnonimine (SIN) in experiments with rats. Applicants’ claims, and the work described by Modin, employ sodium nitrite, *i.e.*, an inorganic nitrite. Applicants respectfully submit that this difference alone renders claims 1-4 and 13-15 non-obvious over Zhang in view of Modin.

For example, according to Dr. Bruce Freeman, “nitric oxide donors and inorganic nitrite are structurally dissimilar and they form NO in distinctly different manners. SNP and SIN release NO directly, whereas sodium nitrite interacts in chemical reactions with heme groups of enzymes and proteins to become metabolized to NO *in vivo*.” Dr. Freeman also does **“not view that inorganic nitrites are equivalent substitutes for recognized nitric oxide donors, such as SNP or SIN, under physiological conditions *in vitro* or *in vivo*”** and indicates that he “would not have understood that inorganic nitrites could substitute for these nitric oxide donors to increase blood flow and reduce brain damage in focal ischemia.” These beliefs are reflective of “the conventional wisdom in the field, especially prior to October 14, 2003.” (See paragraphs 3, 4 and 5 of the Freeman Declaration.) Dr. Freeman’s assertions are echoed by Dr. King (see paragraphs 3 and 4 of the King Declaration).

Thus, the skilled artisan as of the filing date of Applicants’ subject application would not have had an expectation of similar properties for these compounds. Neither Zhang nor Modin equate the activities of sodium nitrite to SNP or SIN, nor do these references teach the interchangeability of these diverse compounds. Indeed, the Declarations of Drs. Freeman and King show that the conventional wisdom in the field at the time did not recognize that inorganic nitrite salt could substitute for SNP or SIP as a nitric oxide donor under physiological conditions.

The Office asserts that SNP and non-acidified sodium nitrite are “well known” as nitric oxide donors and that “even if different mechanisms of action do exist, applicants have not set forth whether this difference does not produce the same result, i.e. nitric oxide donation” (Office action dated April 14, 2009, page 7). The Office appears to base the assertion that non-acidified sodium nitrite is “well known” as a nitric oxide donor on the teachings of Modin. However, Applicants submit that, prior to the priority date of the instant application (October 14, 2003), non-acidified sodium nitrite was not understood to be a nitric oxide donor, particularly under physiological conditions in a subject.

For example, according to Dr. Lundberg, “[p]rior to October 14, 2003, the conventional wisdom among the majority of scientists in the nitric oxide field was that inorganic nitrite was an inert oxidation product of nitric oxide metabolism” (Lundberg Declaration, paragraph 4). Indeed, according to Dr. Freeman, “the overwhelming evidence prior to October 14, 2003, was that non-acidified sodium nitrite was inert and not a vasodilator *in vivo*, particularly in the human circulation, and it was accepted in the pharmacology, chemistry and NO therapeutics fields of research that inorganic nitrite was an

inert oxidation product of nitric oxide metabolism” (Freeman Declaration, paragraph 5). These conclusions are echoed by Drs. Kelm and Ignarro (Kelm Declaration, paragraph 8; Ignarro Declaration, paragraph 8). Thus, the conventional wisdom in the field at the time was that non-acidified sodium nitrite was a *product of nitric oxide metabolism, and **not** a nitric oxide donor*.

Thus, prior to the priority date of Applicants’ instant application, the skilled artisan did not consider non-acidified sodium nitrite to be a NO donor, and certainly did not consider non-acidified nitrite to be a potential substitute for SNP or SIN as a NO donor. For this reason, the skilled artisan, reading Zhang and Modin, would not understand that the sodium nitrite of Modin could function as an “other NO donor” in the methods of Zhang. Therefore, contrary to the position taken by the Office, and as indicated by the Declarations of Drs. King and Freeman, one of skill in this art would *not* have had a reasonable expectation that the inorganic nitrite of Modin could successfully substitute for the nitric oxide donors used by Zhang. Withdrawal of the instant rejection is respectfully requested.

**(2) The aortic ring bioassays used by Modin are not predictive of the *in vivo* effects of sodium nitrite.**

Modin describes aortic ring bioassays, which are experiments performed on **isolated** aortic rings **without circulating blood** (see methods section and Lundberg Declaration, paragraph 3). These experiments are fundamentally different from Applicants’ methods in claims 1-4 and 13-15, which require administration of non-acidified sodium nitrite to a subject (where the sodium nitrite will contact blood). Applicants respectfully submit that this difference alone renders claims 1-4 and 13-15 non-obvious over Zhang in view of Modin.

According to Dr. Kelm, the experimental paradigm used by Modin is a “poor model for predicting *in vivo* function because this ex vivo model utilizes excised rat aorta that is maintained in a modified krebs solution of neutral or acidified pH.” Using the paradigm of Modin, “Most, if not all, of the regulatory factors present in blood that play a physiological role in the vasodilatation process are absent... *Of particular importance is the lack of blood in the aortic ring preparations.* Blood is expected to scavenge nitric oxide, reducing the efficacy of NO and NO donors in blood.” (See Kelm Declaration, paragraph 4; emphasis in original.)

This view is supported by the Declarations of Drs. Ignarro (paragraph 5) and Lundberg (paragraphs 3 and 4). Indeed, Dr. Lundberg (who co-authored the Modin study) states

The experimental model we used in this publication did not include the regulatory factors present in blood, such as hemoglobin in red blood cells, that are known to inhibit the effects of nitric oxide and nitric oxide donor medications. Because of this, our finding that concentrations of non-acidified (pH 7.45) inorganic nitrite greater than 25 micromolar concentration cause vasodilation of excised rat aorta were not considered predictive of whether or not similar concentrations of inorganic nitrite would cause vasodilation under non-acidic/non-hypoxic physiological conditions *in vivo*.

(Lundberg Declaration, paragraph 3). Thus, because of the experimental paradigm used by Modin, one of skill in the art would not understand that the teachings of Modin are applicable to or predictive of what would be observed in an *in vivo* setting. Consequently, there would be no reasonable expectation that the sodium nitrite as employed in Modin would predictably function in the methods provided in Zhang – that is, there was no reasonable expectation that sodium nitrite would work *in vivo* in the presence of blood.

This view was clearly evinced by the Lauer paper – which concludes that “nitrite lacks intrinsic vasodilator action” (see below, in Applicants’ prior response, and the Declarations of Drs. Lundberg (paragraph 4), Kelm (paragraphs 6 and 7), Ignarro (paragraphs 7 and 8) and Freeman (paragraph 5)). One of skill in the art, prior to Applicants’ invention, would have expected that the presence of blood would have **inhibited** the NO generated from nitrite, not increased it. Thus, it is very clear that the results of *in vitro*, blood-free experiments such as those described in Modin are not applicable to an *in vivo* situation.

In addition, the Modin reference itself teaches away from claims 1-4 and 13-15. As indicated in Section 2141.02 of the MPEP, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from the claimed invention. (*W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). Modin teaches that **acidified** inorganic nitrite is preferred, and therefore that non-acidified inorganic nitrite is **not** preferred. The clear teaching of Modin, as acknowledged in the Office’s summary of Modin, is that inorganic nitrite is a more effective vasodilator in an acidic environment as compared to a non-acidic environment. Indeed, Dr. Lundberg -- the senior author of the Modin reference -- believes that inorganic nitrite must be in a “slightly acidic environment (that is, “acidified”) to function effectively as a vasodilator” (Lundberg Declaration, paragraph 3). Thus, if one

of ordinary skill in this art were to consult Modin in relation to Zhang, the only potentially reasonable conclusion to draw from Zhang would be to use inorganic nitrite that is acidified.

Thus, even if, for the sake of argument, the compound used by Modin was deemed a reasonable substitute to the compound used by Zhang (which Applicants do not admit), there is no credible support for an allegation that one of skill would have been motivated to use the sodium nitrite of Modin in the method of Zhang. This is more than a “mere disclosure of more than one alternative” (MPEP 2141.02), but instead the cited references provide a clear teaching away that criticizes, discredits, or otherwise discourages the solution that is now claimed by Applicants. See *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Further, as argued in Applicants response dated March 16, 2009, it has now been clearly shown that oxygenated blood inhibits the nitrite induced vasodilation of aortic rings (Isbell *et al.* (*Am J Physiol Heart Circ Physiol* 293(4):H2565-72, 2007; a copy of which was previously provided to the Office in this file). Thus, it is very clear that the results of *in vitro*, blood-free experiments such as described in Modin are not applicable to an *in vivo* situation. See also Crawford *et al.* (*Blood* 101:566-574, 2006; previously made of record in this file), where the authors conclude that their “data support a function for RBC hemoglobin as an allosterically and redox-regulated nitrite reductase whose “enzyme activity” couples hypoxia to increased NO-dependent blood flow.” (Crawford *et al.*, Abstract.)

Taken together, the arguments and evidence previously made of record, as well as the arguments, Declarations and evidence supplied herein, clearly demonstrate that the skilled artisan would not find claims 1-4 and 13-5 obvious over the teachings of Zhang in view of Modin. Because (1) “nitric oxide donors” (as that phrase is used in Zhang) and sodium nitrite are not equivalent substitutes for each other, and (2) the aortic ring bioassays used by Modin are not predictive of the *in vivo* effects of sodium nitrite, the skilled artisan would fail to include the sodium nitrite of Modin in the “other nitrite donors” of Zhang. Consequently, one of ordinary skill in the art could not have a **predictable and reasonable expectation of success in combining the teachings of the cited references** (Zhang and Modin) to yield Applicants’ invention. Withdrawal of the instant obviousness rejection is respectfully requested.

### *Claim 16*

Although it is not explicitly stated in the Office action, claim 16 appears to be rejected as obvious over Zhang and Modin because these references allegedly inherently include functions that are identical to the instantly claimed invention.

Claim 16 parallels claim 1 in scope but is limited to “administering a non-acidified... salt of nitrite for a sufficient period of time to reach a circulating concentration in blood of the subject of less than about 25  $\mu\text{M}$ ...” This level is below any reasonable threshold one of ordinary skill might have taken from Modin (though Applicants do not admit that Modin provides any reasonable threshold for therapeutic use of non-acidified sodium nitrite). For example, Dr. Lundberg (who supervised the Modin study) and Dr. Kelm (who supervised the Lauer study) conclude that Modin does not teach that non-acidified sodium nitrite is a vasodilator at concentrations of 25  $\mu\text{M}$  or less, *in vitro* or *in vivo*. (Lundberg Declaration, paragraph 3; Kelm Declaration, paragraph 5). Dr. Ignarro, who discovered that nitric oxide relaxes vascular smooth muscle and who has been working in the nitric oxide field for 30+ years (see Ignarro Declaration, paragraph 2 and supporting Exhibit A), concludes that prior to Applicants’ filing “a scientist working in the nitric oxide field would [not] believe that the Modin *et al.* reference teaches that non-acidified inorganic nitrite is a vasodilator at concentrations of 25  $\mu\text{M}$  or less, *in vitro* or *in vivo*.” (Ignarro Declaration, paragraph 6; see also Ignarro Declaration, paragraph 9 and Kelm Declaration, paragraph 9.)

Thus, even if the assays used by Modin were predictive of the *in vivo* effects of sodium nitrite (which Applicants do not admit), one of skill in the art would not predict that non-acidified sodium nitrite at concentrations of 25  $\mu\text{M}$  or less would be vasoactive *in vivo*. Applicants submit that Claim 16 is non-obvious over the cited combination of references (Zhang and Modin) and respectfully request withdrawal of any rejection of this claim for failing the requirements of 35 U.S.C. § 103.

### *Secondary Evidence of Non-Obviousness*

Even if the Office had provided a proper *prima facie* case of obviousness (which Applicants do not concede), secondary indicia of non-obviousness are present that refute the alleged obviousness of Applicants’ claims.



The Supreme Court recognized that “when the prior art teaches away from combining certain known elements [in the prior art], discovery of a successful means of combining them is more likely to be non-obvious.” *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740 (2007), citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966). Indeed, “[k]nown disadvantages... which would naturally discourage search for new inventions may be taken into account in determining obviousness.” *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966). These principles are embodied in Section 2145(X)(D)(3) of the MPEP, which explicitly recognizes that “proceeding contrary to accepted wisdom in the art is evidence of nonobviousness.” *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).”

The instant case is a classic example of “proceeding contrary to accepted wisdom in the art” because (as previously noted) art prior to Applicants’ invention taught that **inorganic nitrite (particularly sodium nitrite) did not have a vasodilatory effect *in vivo***. Art available as of the priority date of the present application taught that administration of pharmaceutical levels of nitrite to human subjects *in vivo* did not induce vasodilation and/or increase blood flow. This is discussed, for instance, at page 2, lines 4-13 and page 21, lines 29-33 of the present specification and supported by the Declarations of Drs. Freeman, Kelm, Ignarro and Lundberg (discussed above and below). Because of the low potency of nitrite in aortic rings without acidification (see, *e.g.*, Modin and Furchgott), and the effects of blood on inhibiting NO, the accepted state of the art as of the priority date of Applicants’ filing was that non-acidified nitrite was not a vasodilator in the human circulation system .

Applicants submit herewith the Declarations of several scientists who were working in the nitric oxide field at the time of the priority date of the instant application, which scientists all agree that the scientific community considered non-acidified sodium nitrite to be inert and not a vasodilator *in vivo*. For example:

1. Dr. Freeman concludes that “the overwhelming evidence prior to October 14, 2003, was that non-acidified sodium nitrite was inert and not a vasodilator *in vivo*, particularly in the human circulation, and it was accepted in the pharmacology, chemistry and NO therapeutics fields of research that inorganic nitrite was an inert oxidation product of nitric oxide metabolism.” (Freeman Declaration, paragraph 5)
2. Dr. Lundberg concludes that “the overwhelming evidence in the scientific literature prior to October 14, 2003, was that near physiological concentrations, non-acidified sodium

nitrite was vasodilator-inactive under normoxic conditions – particularly *in vivo*. Prior to October 14, 2003 the conventional wisdom among the majority of scientists in the nitric oxide field was that inorganic nitrite was an inert oxidation product of nitric oxide metabolism.” (Lundberg Declaration, paragraph 4)

3. Dr. Kelm concludes that “[m]y research group entitled the Lauer *et al.* paper ‘[p]lasma nitrite rather than nitrate reflects regional endothelial nitric oxide synthase activity but lacks intrinsic vasodilator action’ because of our strong belief, based on our research studies and those of others in the field, that plasma nitrite had no physiological effect on vasodilation. I believe, the results of this study were widely accepted at the time by the broad scientific community.” (Kelm Declaration, paragraph 6.)
4. Dr. Ignarro concludes that “[t]he teachings of Lauer *et al.* are consistent with my understanding of inorganic nitrite physiology prior to October 14, 2003... Prior to October 14, 2003, I believed that inorganic nitrite was an inert oxidation product of nitric oxide metabolism. I believe that my understanding of sodium nitrite physiology prior to October 14, 2003 accurately reflects the understanding of researchers working in the field at that time.” (Ignarro Declaration, paragraph 8.)

The Declarants’ statements are supported by the Lauer study (Lauer *et al.*, *PNAS* 98:12814-12819, 2001; previously made of record). This study indicates “Intraarterial application of nitrite was found to be devoid of vasodilator activity at doses up to 36  $\mu\text{M}$ /minute. Venous plasma nitrite concentrations achieved at the highest dose level exceeded 130  $\mu\text{M}$  and were thus approximately 200 times greater than the concentrations measured during maximal eNOS stimulation with Ach” (page 12816, bottom right paragraph). On page 12818 at the bottom right, the authors further claim: “The complete lack of vasodilator activity of intraarterial infusion of nitrite clearly rules out any role for this metabolite in NO delivery.” As noted above, Dr. Kelm, the senior author of Lauer, believes that the results of the Lauer study were widely accepted by the broad scientific community, a conclusion supported by the Declaration of Dr. Ignarro. Additionally, as noted above, the skilled artisan would not have considered the studies of Modin to be predictive of an *in vivo* system. Thus, based on **the *in vivo* teachings** of Lauer related to inorganic nitrite and vasodilation, prior to Applicants’ invention the skilled artisan would not have expected (or predicted) sodium nitrite to have any beneficial therapeutic effect when administered (for instance by injection or inhalation) to a subject to induce vasodilation or increase blood flow, regardless of the *in vitro* results in rat aorta provided by Modin.

The expectations of the skilled artisan are exemplified by the surprise of Drs. Lundberg and Kelm upon the publication of Cosby *et al.* (previously made of record) by the Gladwin group (see Lundberg Declaration, paragraph 4; Kelm Declaration, paragraph 6). In fact, “Cosby *et al.* was met with wide skepticism until the results were reproduced later by a number of other laboratories” (Lundberg Declaration, paragraph 4). The skepticism directed at the Cosby study approached the level of ridicule by others in the field – reflective of there being absolutely nothing obvious or predictable about Applicants’ invention. For instance, the set of Letters to the Editor published in *The New England Journal of Medicine* on July 24, 2003 (349:402-405; previously provided to the Office), comment on Applicants’ earlier work (Schechter & Gladwin, *N Engl J Med* 348:1483-1485, 2003). By way of example, McMahon (at page 403) indicates “The suggestion that nitrite (at native concentrations) causes vasodilation in humans has been refuted experimentally.” (Citing Rassaf *et al.*, 2002). See also Pawlowski (at page 403), which states that “the latter [nitrite ions] has been shown to lack vasoactivity under physiologic conditions.” (Citing Lauer *et al.*, 2001).

Thus, it is clear on the record that those of ordinary (and expert) skill in the art **did not believe that non-acidified sodium nitrite, or any other inorganic nitrite salt, had *in vivo* vasodilatory activity**. Applicants note that “[e]xpressions of disbelief by experts constitute strong evidence of nonobviousness.” MPEP 706.05 citing *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966). Given the above arguments (and those made in the prior response), as well as the evidence and Declarations submitted herewith and previously made of record, Applicants assert that the combination of Zhang and Modin does not make the present invention obvious. These references do not provide any reasonable expectation to one of ordinary skill that they could carry out Applicants’ invention. Withdrawal of the instant obviousness rejection is respectfully requested.

### **Double Patenting Rejection**

Claims 1-4 and 13-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly these claims are unpatentable over claims 1, 6-13 and 20-23 of copending Application No. 10/563,682. Without admitting to the properness of this rejection, Applicants ask that it still be held in abeyance until the claims of one case or the other are allowed.

Applicants will provide the Examiner with copies of any prosecution documents from Application No. 10/563,682 on request, though the prosecution documents are available on PAIR.

**Conclusion**

In view of the foregoing, Applicants believe the pending claims are in condition for allowance, which action is courteously requested.

If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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